

I concur with this review memo. A. Wensky. 7/2021

**FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
Division of Clinical Evaluation and Pharmacology/Toxicology
Pharmacology/Toxicology Branch**

BLA NUMBER: STN #125703.091

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PRODUCT: KTE-X19 (brexucabtagene autoleucel; TECARTUS™)

APPLICANT: Kite Pharma Inc
PROPOSED INDICATION: For the treatment of adult patients with relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (B-ALL)

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EXECUTIVE SUMMARY:

KTE-X19 (also referred to as axicabtagene ciloleucel) is an autologous chimeric antigen receptor (CAR) T-cell product engineered with a retroviral vector to express an anti-CD19 single-chain

antibody fragment that is linked to CD3 ζ and CD28 T-cell activating domains. This product uses the same retroviral vector and anti-CD19 CAR transgene as the applicant's approved product, axicabtagene ciloleucel (YESCARTA™; BLA #125643) and is currently approved for mantle cell lymphoma (MCL). With this supplemental Biologics License Application (sBLA), the applicant aims to seek approval for use of KTE-X19 to treat B-ALL. The proposed dose level for patients with B-ALL is 1×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 1×10^8 CAR-positive viable T cells.

In this supplement, the applicant has provided updated vector integration analysis using axicabtagene ciloleucel (Module 4) and discussion of literature and relevant nonclinical data (Module 2.4 and 2.6). The integration profile was found to be consistent with published data for similar vectors which suggests a relatively low risk for malignant transformation of T cells by retroviral vectors. Traditional *in vitro* and *in vivo* genotoxicity and carcinogenicity/tumorigenicity assessments of KTE-X19 were not conducted which is acceptable based on the product characteristics, safety profile and indication.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

The updated nonclinical information provided in this supplement does not raise additional safety concerns that may impact approval of the sBLA. There were no nonclinical deficiencies identified in this submission and no outstanding requests for additional nonclinical data. The nonclinical information provided in this submission supports approval of the sBLA.

Formulation and Chemistry:

The active substance of KTE-X19 consists of autologous T cells that have been genetically modified *ex vivo* to express a CAR that targets CD19. The active substance of KTE-X19 is produced using the patient's T cells that have undergone *ex vivo* (b) (4) T cell enrichment using a (b) (4). The enriched T cell population is activated by stimulation with immobilized anti-CD3 monoclonal antibodies (mAb) and soluble anti-CD28 mAb in the presence of interleukin (IL)-2. Activated T cells are transduced with a replication-deficient retroviral vector ((b) (4)). The engineered, autologous T cell product is formulated in a cryopreservation medium suitable for infusion and is supplied cryopreserved at a temperature of $\leq -150^\circ\text{C}$. Each cryostorage bag contains 1×10^6 anti-CD19 CAR T cells/kg in a nominal volume of 68 mL ((b) (4) of CryoStor (b) (4) of Sodium Chloride ((b) (4)) and (b) (4) of human Albumin (b) (4)).

Abbreviations

ASCT	autologous stem cell transplant
B-ALL	B-cell precursor acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CLL	chronic lymphocytic leukemia
DART	developmental and reproductive toxicity
DNA	deoxyribonucleic acid
IL	interleukin
kD	kiloDalton
kg	kilogram
MCL	mantle cell lymphoma
mL	milliliters
NGS	next generation sequencing
NHL	Non-Hodgkin lymphoma
P/T	pharmacology/toxicology
r/r	relapsed or refractory
sBLA	supplemental biologics license application
scFv	single chain variable fragment
VIS	vector integration site
(b) (4)	Kite CAR T-cell manufacturing process that uses isolated (b) (4) T cells collected from the donor as starting material.

Related File(s)

BLA 125643 [APPROVED] YESCARTA™, an engineered autologous T cell immunotherapy, is indicated for the treatment of adult patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant (ASCT) held by Kite Pharma Inc.

IND 16675 [ACTIVE] Autologous Peripheral Blood T Cells (b) (4) and IL-2, CD3, and CD28 Activated Transduced with Retroviral Vector (b) (4) Expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-C19 CAR); and Cultured with Cytokines; Following CSF Prophylaxis, Bridging Chemotherapy as needed, Fludarabine, and Cyclophosphamide, held by Kite Pharma Inc.

IND #16278 [ACTIVE] KTE-C19; Autologous Peripheral Blood T Cells Transduced with Retroviral Vector (b) (4) Expressing anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR); and Cultured with Cytokines; Following Fludarabine and Cyclophosphamide, held by Kite Pharma, Inc.

(b) (4)

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INTRODUCTION

KTE-X19 is an autologous CAR T cell product indicated for the treatment of relapsed or refractory (r/r) B-ALL in adult patients.

T cells that are genetically modified to express a CAR can target specific tumor antigens and elicit an anti-tumor response. Potential mechanisms of anti-tumor activity include direct killing of tumor cells with effector molecules and secretion of various cytokines that potentiate and sustain the cytotoxic response in addition to promoting T cell survival.

KTE-X19 was designed to target CD19-expressing B cell malignancies. CD19 is a 95 kD transmembrane protein that is expressed in all normal B cells and in B cell malignancies including all subtypes of B-cell non-hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL). B-ALL is the most common type of ALL in which too many B-cell lymphoblasts are found in the blood and bone marrow. CD19 is not found in pluripotent hematopoietic stem cells or in most plasma cells.

NONCLINICAL STUDIES

Note: Data from integration analysis using brexucabtagene autoleucel was provided in the original BLA submission (please see P/T memo for more details); this supplement contains an updated analysis of this data. No new pharmacology, pharmacokinetic or toxicology studies were submitted.

PHARMACOLOGY STUDIES

No new pharmacology studies were conducted. Please see clinical reviewer’s memo for clinical efficacy data supporting the use of KTE-X19 for B-ALL.

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies were conducted.

PHARMACOKINETIC STUDIES (biodistribution)

No pharmacokinetic studies were conducted.

TOXICOLOGY STUDIES

No new toxicology studies were conducted. Please see clinical reviewer's memo for clinical safety data supporting the use of KTE-X19 for B-ALL.

Developmental and Reproductive Toxicology Studies (DART)

No DART studies were conducted.

Genotoxicity Studies

Traditional genotoxicity studies were not conducted using KTE-X19, however, given the use of a murine γ -retroviral vector to stably integrate the anti-CD19 CAR into the T cell genome, a risk associated with insertional mutagenesis exists. In addition to an updated discussion of published literature and clinical trial ZUMA-2, the applicant provided summary data from an updated integration analyses conducted using axicabtagene ciloleucel (Module 4.2.3.3.2).

Integration Site Analysis

Methods: As reported in the original BLA submission, T cells from 3 healthy donors with transduction rates of (b) (4) for Donor 1, 2 and 3 respectively were used. Five cell aliquots per donor product were analyzed, each containing approximately 500,000 T cells (analysis was performed using transduced and non-transduced T cells present in the product). Genomic DNA (100 ng) extracted from each aliquot was subjected to next generation sequencing (NGS). Vector integration sites (VIS) were identified using (b) (4)

Contrary to the (b) (4) analysis used in the original BLA submission, in the updated report, the (b) (4) was used to identify the retroviral long-terminal repeat (LTR) sequences and the genomic coordinates of sequences adjacent to the LTR. Each VIS was quantified by (b) (4)

Results: The overall conclusions were the same as those originally reported in the original BLA submission. Briefly, there was no indication of dominant VIS that would suggest an advantage for clonal expansion, however, there was a low frequency of integration events in exons that may suggest a potential for gene disruption. Preferential integration was noted within close proximity to TSS and transcriptionally active T cell genes consistent with published data. Similar results were observed previously using other retrovirally transduced T-cell products.

Carcinogenicity/Tumorigenicity Studies

No carcinogenicity/tumorigenicity studies were conducted.

APPLICANT'S PROPOSED LABEL

No P/T changes were made to the applicant's proposed labeling for Sections 8 and 13.

CONCLUSION OF NONCLINICAL STUDIES

No significant safety concerns were identified during the review of nonclinical studies. The nonclinical data support approval of the sBLA.

KEY WORDS/TERMS

KTE-X19, anti-CD19 CAR T cells, chimeric antigen receptor, CAR, B cell aplasia, B cell malignancy, retroviral vector, T cells, axicabtagene ciloleucel, YESCARTA™, TECARTUS™